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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/904,099	07/11/2001	Geetha Shankar	10602-013-999	1334

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Pennie & Edmonds, LLP
3300 Hillview Avenue
Palo Alto, CA 94304

EXAMINER
ULM, JOHN D

ART UNIT	PAPER NUMBER
1646	15

DATE MAILED: 09/26/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/904,099	Applicant(s) Shanker et al.
	Examiner John Ulm	Art Unit 1646

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *Jul 10, 2003* .

2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *1-27* is/are pending in the application.

4a) Of the above, claim(s) _____ is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *1-27* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

1) Claims 1 to 27 are pending in the instant application. Claims 22 to 27 have been added as requested by Applicant in Paper Number 14, filed 10 July of 2003.

2) Any objection or rejection of record that is not expressly repeated in this action has been overcome by Applicant's response and withdrawn.

3) The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

4) Tables 1 to 6 of the instant specification do not comply with 37 C.F.R. 1.52 (b) with respect to line spacing. 37 C.F.R. 1.52 (b) states that "The lines of the specification, and any amendments to the specification, must be 1½ or double spaced". 37 C.F.R. 1.58(c)states that "Chemical and mathematical formulae and tables must be presented in compliance with §1.52(a) and (b), except that chemical and mathematical formulae or tables may be placed in a landscape orientation if they cannot be presented satisfactorily in a portrait orientation". The lines in the tables are single spaced. Correction is required.

5) Claims 1 to 27 are rejected under 35 U.S.C. 103(a) as being unpatentable over the Ancellin et al. publication (J. BIOL. CHEM. 274(27):18997-19002, 02 Jul. 1999) in view of any two or more of the Conway et al. (J. BIOL. CHEM. 275(27):20602-20609. 07 Jul. 1999), Schöth et al. (MOL. PHARM. 54:154-161, 1998), Wu et al. (J. BIOL. CHEM. 272(14):9037-9042, 04 Apr. 1997), Meng et al. (EUR. J. PHARM. 311:285-292, 1996), Holtmann et al. (J. BIOL. CHEM. 270(24):14394-14398, 16 Jun. 1995), Takagi et al. (J. BIOL. CHEM. 270(17):10072-10078, 28 Apr. 1995), Buggy et al. (J. BIOL. CHEM. 270(13):7474-7478, 1995), Kim et al. (J.

BIOL. CHEM. 269(46):28724-28731, 28 Nov. 1994), Gether et al. (J. BIOL. CHEM. 268(11):7893-7898, 15 Apr. 1993) and Kobilka et al. (SCIENCE 240:1310-1316, 03 Jun. 1988, cited by Applicant) publications for those reasons of record as applied to claims 1 to 21 in the previous office action. As stated therein, the instant claims are drawn to a chimeric Edg receptor comprising domains from Edg1 and Edg3, and an assay employing it. The Ancellin et al. publication taught that Edg-1, Edg-3 and Edg-5 were structurally related G protein-coupled receptors having similar but distinct pharmacological characteristics and that they were involved in the regulation of specific biological processes by coupling to discrete signaling pathways. Ancellin et al. did not describe chimeric receptors. Each of the Conway et al. (Figure 3), Schöth et al. (Figure 2), Wu et al. (Figure 1), Meng et al. (Tables 1 to 3), Holtmann et al. (Figures 1 and 6), Takagi et al. (Figure 2), Buggy et al. (Figure 2), Kim et al. (Table 1, Figures 2, 5 and 6), Gether et al. (Table 1, Figures 1 and 2) and Kobilka et al. (Figures 1 to 3 and 5 to 8) publications described the construction of a series of chimeric G protein-coupled receptors composed of various combinations of structural domains from two different but related G protein-coupled receptors having distinct pharmacological properties for the purpose of identifying those structural domains in each of those two related receptors that are responsible for the specific pharmacological properties of that receptor. Because the Ancellin et al. publication disclosed that Edg-1 and Edg-3 were two structurally related but pharmacologically distinct G protein-coupled sphingosine 1-phosphate receptors, an artisan of ordinary skill in the art of G protein-coupled receptor biology would have found it *prima facie* obvious to have constructed a series of chimeric

Edg receptors composed of various combinations of transmembrane, intracellular and extracellular domains from Edg-1 and Edg-3 for the purpose of identifying those structural domains in each of those two related receptors that are responsible for the specific pharmacological properties of that receptor

Applicant has traversed this rejection on the premise that nothing in the combination of cited references teaches or suggests the Edg chimeras cited in any of claims 1 to 21. Essentially, Applicant argues that none of the secondary references discuss Edg receptors and ignores the premise upon which they were relied, which is that a combination of any two or more of these references shows that the technique of constructing of a series of chimeric G protein-coupled receptors composed of various combinations of structural domains from two different but related G protein-coupled receptors having distinct pharmacological properties for the purpose of identifying those structural domains in each of those two related receptors that are responsible for the specific pharmacological properties of that receptor was a routine practice in the art of studying the molecular biology of G protein-coupled receptors prior to the time that the instant invention was made. In arguing against the references individually, Applicant cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

Applicant urges that the secondary references teach away from the claimed chimera because "the large majority of the chimeric GPCRs in references cited by the Patent Office

comprise transmembrane domain substitutions of a GPCR, in contrast to the specific intracellular domain chimeras of claim 1". Applicant is factually incorrect. If one ignores the "Edg" limitation of claim 1, it encompasses a chimeric G protein-coupled receptor comprising at least one extracellular and transmembrane domain from a first receptor and at least one intracellular domain from a second receptor. Ten of the fourteen chimeric receptors described in Figure 3 of Conway et al., six of the eight chimeric receptors described in Figure 2 of Schioth et al., three of the six chimeric receptors described in Figure 1 of Wu et al., seven of the twenty three chimeric receptors described in Meng et al., two of the six chimeric receptors described in Figure 1 of Holtmnann et al., five of the six chimeric receptors described in Figure 2 of Takagi et al., six of the ten chimeric receptors described in Figure 2 of Buggy et al., four of the six chimeric receptors described in Figure 2 of Kim et al., three of the five chimeric receptors described in Figure 1 of Gethjer et al. and nine of the ten chimeric receptors described in Figure 1 of Kobilka et al. meet the structural limitations of claim 1. Because a substantial number of chimeric receptors that were described in the secondary references of record met the structural requirements of the instant claims, Applicant's argument that those references taught away from the claimed configuration is not supported by the preponderance of evidence of record.

Applicant appears to be urging that the limitation "chimeric intracellular domain" is a distinguishing limitation of the instant claims. It is unclear if this limitation applies to the chimeric receptors identified as "Edg 1/3(ct)" and "Edg 8/4 (ct)" as recited in claim 10. It is also unclear how this limitation distinguishes over the chimeric receptors identified as CR3, CR4, CR5 and

CR10 in Kobilka et al., for example. Applicant argues that "the chimeras of Kobilka *et al.* comprise substituted structures altogether different from the chimeric intracellular domain described by Applicants". Applicant states that "Kobilka et al. do not teach or suggest a chimeric receptor wherein the extracellular domain and transmembrane domain of a first GPCR are linked to a chimeric intracellular domain comprising a intracellular strand of a second GPCR". To the contrary, this is exactly the configuration described as CR3, CR4, CR5 and CR10 in Kobilka et al.

The particular embodiments of the instant invention identified as "Edg 1/3(i3ct)", "Edg 1/3(i2i3ct)" and "Edg 5/3(i3ct)" are free of the prior art. However, the instant claims, in their current form, do not reflect a general inventive concept lacking from the prior art. The requirement for an extracellular domain of a first Edg receptor operably linked to a transmembrane domain from that same receptor merely requires the presence of an extracellular domain and any transmembrane domain from that same receptor be present in a chimeric protein. The vast majority of the chimeric G protein-coupled receptors that are described in the art of record comprise the extracellular domain and at least the first transmembrane domain from a first receptor joined to the remainder of a second receptor. The "operably linked" limitations of the instant claims are not distinguishing simply because all of the components in a chimeric G protein-coupled receptor are usually "operably linked" to one another. The limitation "chimeric intracellular domain" is problematic because it is unclear if it is referring to an intracellular domain from a chimeric receptor or an intracellular domain comprising portions from the corresponding domain of different receptors. Further, because the boundaries between the intracellular,

extracellular and transmembrane domains of a G protein-coupled receptor are not exact, many of the chimeric G protein-coupled receptors described in the prior art comprise "chimeric intracellular domains" because the junction between the chimeric regions of each of those receptors occurs within a intracellular domain, even if by only a few amino acid residues. The instant specification does not disclose any particular advantage to be realized from the replacement of only a few amino acids within, for example, the first cytoplasmic (intracellular) of a chimeric Edg receptor.

The chimeric receptors identified as "Edg 1/3(i3ct)", "Edg 1/3(i2i3ct)" and "Edg 5/3(i3ct)", which are patentable, have a specific utility because they each contain a very specific combination of domains from two different Edg receptors and these specific combinations are not reflected in the instant claims. "Edg 1/3(i3ct)", for example, doesn't just comprise an extracellular and transmembrane domain from a first receptor and a chimeric cytoplasmic domain from a second receptor. It comprises the entire amino acid sequence from a first edge receptor up to the third cytoplasmic loop, including the extracellular domain, the first five transmembrane domains and the first two extracellular loops from that first receptor. "Edg 1/3(i3ct)" has only been altered in its third cytoplasmic loop and by the non-contiguous replacement of its fourth cytoplasmic domain. It is this **non-contiguous** replacement of the third and fourth cytoplasmic domains in "Edg 1/3(i3ct)" which distinguishes it from the chimeric configurations identified as CR3, CR4, CR5 and CR10 of Kobilka et al. "Edg 1/3(i3ct)" is patentable because it has had only very specific portions of a first edge receptor replaced with corresponding portions from a second

edge receptor and it is these specific domain swaps within an Edg receptor that are not suggested by the prior art. However, the novel elements which define the general structural configurations which distinguish "Edg 1/3(i3ct)", "Edg 1/3(i2i3ct)" and "Edg 5/3(i3ct)" from the prior art are not present in the instant claims.

6) Applicant's arguments filed 10 July of 2003 have been fully considered but they are not persuasive for those reasons given above.

7) **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to John D. Ulm whose telephone number is (703) 308-4008. The examiner can normally be reached on Monday through Thursday from 8:30 AM to 5:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Yvonne Eyler can be reached at (703) 308-6564.

Official papers filed by fax should be directed to (703) 308-4242 or (703) 872-9306. Official responses under 37 C.F.R. § 1.116 should be directed to (703) 872-9307.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

JOHN ULM
PRIMARY EXAMINER
GROUP 1800